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The renin-angiotensin system and hypertension

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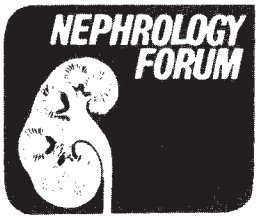

Case presentation

A 28-year-old man first became aware of elevated blood pressures during his early teens because he was often told that his blood pressure was "high" during routine preemployment physical examinations. Five years ago, he noted episodic confusion, dizziness, blurring of vision, slurring of speech, epistaxis, and occipital headaches, but did not consult a physician. One year later, he was seen in an infirmary while in the army and his blood pressure was 180/130 mm Hg; methyldopa in a dosage of 1 g daily was prescribed. Shortly thereafter, he suffered a hypertensive crisis with encephalopathy. His blood pressure at that time was 240/160 mm Hg. Evaluation for hypertension was carried out at an army medical center. An i.v. urogram revealed only an enlarged (17.5 cm) left kidney with otherwise normal architecture and function. A renal scan, sonogram, and cytoscopic examination failed to reveal evidence of a right kidney, and it was thought to be congenitally absent. Results of urinalysis were normal, 24-hour urine protein excretion was 9 mg, and the endogenous creatinine clearance was 87 ml/min. Chest radiograph and electrocardiogram (EKG) were normal. The serum creatinine concentration was 1 mg/100 ml. On several determinations, normal laboratory values were found for serum electrolytes, calcium, and uric acid, thyroid function, blood sugar, and 24-hour excretion of vanillylmandelic acid (VMA), metanephrines, and catecholamines; the Regitine test was negative on two occasions.

Over the next 2 years, the patient had three additional hypertensive crises with a residual mild right hemiparesis, dysarthria, and a right superior temporal visual field defect. Treatment with a variety of medications including diuretics, methyldopa, guanethidine, propranolol, clonidine, and hydralazine yielded relatively poor control of the patient's hypertension.

Two years ago, he was admitted to the New England Medical Center Hospital (NEMCH) with exertional angina, paroxysmal nocturnal dyspnea, orthopnea, episodic dizziness, and dysarthria. The patient's history revealed that he had smoked about 10 cigarettes per day for 6 years, and that both parents and his only sibling were hypertensive. Physical examination revealed the following data: blood pressure, 170/115 mm Hg; optic fundi, mild arteriolar narrowing; cardiac examination revealed normal S1 and S2, an S4 at the apex, and a Grade II/VI systolic ejection murmur that radiated to the carotid arteries and was best heard at the lower left sternal border; abdominal examination revealed no epigastric or flank bruits; peripheral pulses were intact and synchronous with no bruits; neurologic examination revealed evidence for a cerebral infarction in the region of the left middle cerebral artery and anterior cerebral artery. The remainder of the examination was normal. Laboratory findings revealed the following data: serum creatinine, 1.2 mg; blood urea nitrogen (BUN), 15 mg/100 ml; hemogram, serum electrolytes, plasma lipids, AM and PM cortisols, T4 and T3 uptake, serum calcium, serum phosphorus, total serum protein, serum albumin, serum bilirubin, blood glucose, serum uric acid, transaminases, and several determinations of urinary VMA, metanephrines, and catecholamines were within normal limits; urine cultures showed no growth; urine sediment was unremarkable; peripheral plasma renin activity (PRA) on an 80 mEq sodium diet and following 4 hours in the upright position was 12.2 ng/ml/hr; chest radiogram was within normal limits; EKG showed incomplete right bundle-branch

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block but no other abnormalities; i.v. urogram revealed the left kidney to be 18 cm in length with a normal nephrogram and collecting system, but there was no evidence of a right kidney; computerized tomographic (CT) scan of the abdomen showed no evidence of a right kidney; electroencephalogram, brain scan, CT scan of the head, and lumbar puncture were within normal limits. The recent neurologic symptoms were thought to represent transient ischemic attacks; anticoagulants were not given. Satisfactory blood pressure control was achieved on a daily regimen of clonidine (0.8 mg), propranolol (120 mg), hydrochlorothiazide (100 mg), and spironolactone (100 mg).

After discharge, the patient continued to experience exertional chest pain relieved by rest and nitroglycerin, episodic dizziness, dysarthria, and paroxysmal nocturnal dyspnea. One and one-half years ago, he had another hypertensive crisis associated with loss of consciousness, which was treated successfully with diazoxide at another hospital. He was readmitted to NEMCH 1 year ago with uncontrolled hypertension (180/120 mm Hg) while on a regimen of clonidine, propranolol, guanethidine, hydrochlorothiazide, and spironolactone. The physical examination was unchanged from the earlier admission. The serum creatinine concentration was 1.1 mg, and the BUN concentration was 12 mg/100 ml. An EKG showed an incomplete right bundle-branch block, a chest radiograph was normal, and an echocardiogram showed mild left ventricular hypertrophy. Minoxidil was added to the therapeutic regimen, and guanethidine was discontinued. At discharge, the blood pressure was 124/94 mm Hg.

The patient continued to experience episodes of severe occipital headache associated with neck stiffness, diaphoresis, dizziness, blurring of vision on the right side, and slurred speech; blood pressures taken at home during these episodes were 170-190 systolic to 120-124 diastolic mm Hg. The daily therapeutic regimen included minoxidil (40 mg), clonidine (0.8 mg), propranolol (400 mg), and furosemide (80 mg).

Eight months ago, the patient was readmitted to NEMCH. While following the above drug regimen, blood pressures were 150-190 systolic to 100-120 diastolic mm Hg. Physical examination was unchanged. The serum creatinine concentration was 1 mg, and the BUN was 13 mg/100 ml. Chest radiograph and EKG were unchanged. A renal arteriogram revealed a single left kidney with no abnormalities of the major left renal artery, an accessory artery to the lower pole, or their branches; there was some minimal irregularity of the distal intrarenal branches; there was no evidence of a right renal artery or kidney. Venous sampling for measurement of PRA was obtained from several sites with the following results: lower inferior vena cava, 8.3; left main renal vein, 19.6; left upper venous branch, 13.2; midleft venous branch, 10.3; and lower left venous branch, 24.9 ng/ml/hr.

Discussion

DR. E. HABER: This patient presents a most unusual and interesting problem. The pertinent facts are that the patient is a young man of 28 years who is known to have had an elevated blood pressure since his early teens, that is, for more than 10 years; he had symptoms for at least 5 years that included hypertensive encephalopathy on several occasions, resulting in residual neurological deficits, hemiparesis, dysarthria, and a visual field defect, as well as angina pectoris. Indeed, this patient's course represents a telescoped history of the ravages of hypertension. The normal findings on cerebral CT scan may well indicate lacunar disease, and if the patient's symptoms truly represent angina pectoris he also has significant coronary artery stenosis. The family history is of special interest in that both parents and a sibling also suffer from hypertension. The patient's blood pressure has been remarkably resistant to treatment. Sympatholytics, vasodilators, and diuretics were administered with little lasting benefit. Typically, adequate blood pressure control was attained in the hospital setting, but shortly thereafter the patient reappeared with markedly elevated systolic and diastolic pressures.

I would like to concentrate first on a detailed discussion of the patient's problem, particularly with respect to narrowing the possible causes of his hypertension, and then turn to a more general discussion of the issue suggested by this case. Physicians are most often interested in mechanisms, particularly mechanisms that can be explained on the basis of pathophysiology. It is for this reason that an almost undue amount of attention is focused on secondary causes of hypertension, when they may be implicated at most in 5% of patients who present with elevated blood pressure. The first sensible question to address is whether or not this patient has reached the accelerated or malignant stage of essential hypertension. In favor of this diagnosis is the very strong family history of hypertension.

Perhaps the most apt description for accelerated hypertension is a state in which end organ damage is compressed into a brief time period. This manifestation occurs in approximately 1% of hypertensive patients, usually in those whose disease is poorly controlled or untreated. The renin system is believed to play a major role in the development of malignant hypertension though patients with malignant hypertension and normal PRA have been reported rarely. In this patient, the sole chemical abnormality uncovered in the course of a very extensive laboratory evaluation was an increase in PRA. Patients with malignant hypertension characteristically have severe hypertension, focal neurological deficit, left ventricular failure, and myocardial is-

chemia, all of which this patient manifests. Most patients with malignant hypertension also have renal failure, notably absent here.

Although it is difficult to exclude accelerated hypertension as the primary diagnosis, certain anatomical features uncovered on contrast radiography suggest that secondary hypertension should be considered carefully. The causes of secondary hypertension that could reasonably be listed in a differential diagnosis in this patient include coarctation of the aorta, pheochromocytoma, primary parenchymal renal disease, primary aldosteronism, and hyperreninemia secondary to an intrarenal lesion. This patient's comprehensive examination allows me to exclude most of these possibilities. A creatinine clearance of 87 ml/min in the presence of a single kidney with normal values for BUN and serum creatinine, minimal urinary protein content, and an unremarkable urine sediment makes parenchymal disease a most unlikely cause of chronic hypertension. The elevated renin activities immediately serve to exclude primary aldosteronism, which is always associated with depressed renin activity. Normal urinary excretions of catecholamines, VMA and metanephrine eliminate the possibility of pheochromocytoma presenting as nonparoxysmal hypertension. The observation during the physical examination that pulse delays were not observed and the presence of normal chest radiograms without characteristic rib notching or other pathognomonic signs exclude coarctation of the aorta.

I must then focus on the renal anatomical abnormality and the elevated PRA. First, I must be convinced that there is not a very small shrunken kidney on the right side, which is not manifesting its presence in any way except by excess renin secretion. The data gathered indicate that a right kidney was not detected by i.v. urography, by angiography, by renal scan, by cystocopy—presumably no ureter was seen—by sonography, and ultimately by body CT scan. All of these methods could miss a very small kidney of minimal excretory function. It might be seen only by selective renal venography [1]. There is one finding, however, that tends to exclude such a kidney as the primary source of hyperreninemia. It is characteristic that when the major contribution of elevated PRA is from one kidney, the contralateral normal kidney is marked by suppression of renin secretion. Yet, what was found was an abnormally elevated renin excretion from the left main renal vein (19.6 ng/ml/hr). If there had been a cryptic right kidney producing renin, I would have expected the concentration of renin in the left main renal vein to be close to that of the lower inferior vena cava. Whether there is a right kidney producing renin in addition to the overproduction of renin in the left kidney unfortunately cannot be ascertained because we do not have a vena cava sample above the renal veins. If there were still further augmentation of renin concentration at that sampling point, a renin secreting right kidney could be postulated.

The focus of interest and the most likely pathogenetic factor in the hyperreninemia is the sole large left kidney. The lower left venous branch of this kidney contributes twice as much renin activity (24.9 ng/ml/hr) as the upper branch (13.2 ng/ml/hr) and the midbranch (10.3 ng/ml/hr). If one were comparing the arteries of two contralateral kidneys rather than branches of a single kidney's arteries, these differences would satisfy most criteria for the diagnosis of unilateral renovascular hypertension. Thus, the most interesting question is whether or not the lower pole of the single kidney could be responsible for renin-dependent hypertension in this patient, and, if so, what are the possible etiologies.

Although I have not found a report of a unilateral single kidney, only a part of which was contributing to renin-dependent hypertension, such reports are common when two kidneys are present [2]. Perhaps the best precedent for a hyperreninemic lesion in a single kidney is the report by Golden et al [3] of a patient with hypertension who was shown to have stenosis of the right renal artery of a single horseshoe kidney. Renin activity in the right renal vein was more than twice that of the left renal vein.

Schambelan et al [2] identified 14 patients in whom selective renal vein sampling uncovered segmental lesions contributing to a hyperreninemic syndrome. Diagnoses included segmental infarction, renal artery branch stenosis, and renin-secreting tumor. Other potential causes of segmental renal lesions that could be responsible for hyperreninemia include renal artery dissection, intrarenal vascular abnormalities, renal cyst, and congenital segmental renal hypoplasia. The availability of a good renal angiogram allows me to relegate some of these diagnoses to a low order of probability.

Spontaneous renal artery dissections occurring in hypertensive patients [4] are a cause of renal artery stenosis but, again, should be reasonably apparent in the relatively large branches of the main renal artery. Babka, Cohen, and Sode [5] reported a solitary renal cyst associated with renin-producing hypertension. The cyst was large, however, and readily identified on contrast studies. Segmental renal

infarcts must also be considered but are usually readily seen on angiography. Segmental renal hypoplasia, the Ask-Upmark syndrome, has been documented as a cause of renin-dependent hypertension. Royer et al [6] reviewed 36 cases of this syndrome in which the patients first presented between 8 and 20 years of age. Although females predominated, 11 of the 36 patients were male; all were hypertensive. In 1 of these patients, only the upper segment of a single kidney was affected and its surgical removal resulted in cure of hypertension. The Ask-Upmark kidney does, however, present a rather clear-cut radiologic picture [7]. The excretory urogram may show a nodular configuration of the kidneys with a distorted pelvocalylceal pattern indicating varying degrees of dilatation, elongation, and compression. Displacement of calyces is probably due to compensatory hypertrophy of intervening renal tissue. Arteriogram shows displacement of interlobar and arcuate branches by the same masses of regenerating renal tissue. None of these findings was apparent on review of the angiogram in this patient, so this diagnosis can readily be excluded.

It is not possible, however, to exclude the diagnosis of a renin-secreting tumor. One of the first patients described by Robertson et al [8] was a 16-year-old boy who presented with severe hypertension that was unresponsive to treatment. Both an i.v. urogram and a renal angiogram were entirely normal. A tumor was not discovered until a second laparotomy was performed; at which time, its removal resulted in a cure of hypertension. A very well-studied case reported by Conn et al [9] was also characterized by a very subtle presentation of the tumor on the angiogram. It was missed at the time of the first angiogram when the patient was already markedly hypertensive; it was seen on a second angiogram 2 years later. At nephrectomy, the tumor was very difficult to visualize from the kidney surface. Five patients reviewed by Conn et al [9] manifested hypertension for periods of 9 months to 6 years prior to operative cure. The patients were between 16 and 37 years old at the time the definitive diagnosis was made. Most renin-secreting tumors are benign lesions arising from juxtaglomerular cells, though an occasional Wilms' tumor may secrete significant quantities of renin [10]. Thus, a small renin-producing tumor in the lower pole cannot be excluded on the basis of the data available.

A branch renal artery stenosis should be seen rather readily although an asymmetric lesion might be missed in a single view. At this patient's age the etiology would most likely be fibromuscular hyperplasia, which does tend to be more symmetrical within a vessel as opposed to the classical asymmetry of atherosclerotic plaques.

How should one proceed in the treatment of this 28-year-old man who has already suffered the ravages of hypertension in a compressed and accelerated course? Medical management has been remarkably unsuccessful considering all of the antihypertensive drugs available for routine clinical use. Are the drugs or drug combinations used ineffective, or is lack of patient compliance outside the hospital the cause of poor control? The treatment of hypertension requires close patient cooperation, and unwillingness to follow a prescribed program has been documented as a frequent cause of therapeutic failure [11]. Regardless of the reasons for ineffective medical management, however, what additional diagnostic tests might be performed to reveal a surgically remediable lesion? Would a surgical attack be justified in a patient with a single kidney? Is there an alternative to partial nephrectomy or bypass surgery?

Source of renin and control of its secretion

I should now like to turn to discussion of the renin system and its role in normal and pathologic blood pressure control in order to put this patient's problems in perspective. Renin is synthesized and stored in membrane bound cytoplasmic granules by cells at the vascular pole of the renal glomerulus [12, 13]. Both the afferent and efferent arterioles are anatomically and functionally associated with a group of specialized cells at the origin of the distal tubule that forms the macula densa. The entire structure is referred to as the "juxtaglomerular apparatus." This site is the center of a feedback loop, which serves to regulate blood pressure and probably intravascular volume by modulating the rate of renin secretion. Factors directly affecting the rate of secretion of renin by the juxtaglomerular apparatus include sodium concentration in the distal tubule, blood pressure in the afferent arteriole, plasma angiotensin II concentration, and the impulse traffic of the renal sympathetic nerves.

The secretion of renin ultimately results in the production of angiotensin II, which has both direct and indirect effects on blood pressure and blood volume. Angiotensin II is a potent vasoconstrictor, thereby directly raising blood pressure. It also acts on the central nervous system to increase peripheral vascular resistance. The adrenal gland may be stimulated by angiotensin II or its metabolic product, angiotensin III, to produce aldosterone, a potent mineralocorticoid that promotes sodium retention in the renal tubule. Sodium retention, in turn,

increases vascular volume and blood pressure.

The feedback loop is completed when vasoconstriction and sodium retention increase blood pressure and decrease renin secretion by acting directly on the baroreceptors in the juxtaglomerular apparatus. Stimulation of a chemoreceptor for sodium in the kidney and several vascular baroreceptors located elsewhere in the circulation also serve to regulate renin secretion. These concepts are reviewed in considerably more detail elsewhere [14].

Chemistry of the renin-substrate reaction

Renin has no known direct physiologic effect but acts only to cleave its substrate, angiotensinogen, which is an alpha II globulin synthesized in the liver. The amino acid sequence of the amino terminal 14 residues of renal substrate is known (Fig. 1). Renin cleaves between two leucine residues at position 10 and 11 to release the decapeptide angiotensin I. Angiotensin I is in turn cleaved between residues 8 and 9 by a converting enzyme to yield the active pressor hormone, angiotensin II. Aminopeptidases further degrade angiotensin II by removing the amino terminal aspartic acid. The resultant heptapeptide, sometimes called angiotensin III, is believed by some investigators to be the primary mediator of adrenal cortical aldosterone secretion [15, 16]. Angiotensin II and III have very short half-lives in the circulation and are further degraded to smaller inactive peptides [17].

The past several years have seen the development of interest concerning possible renin precursors or zymogens. A number of observations have been made that on the surface appear contradictory. In evaluating various reports two critical questions which must be kept in mind are (1) What is the precise definition of renin? and (2) Is the enzyme that is examined in vitro the same material that is produced in vivo by the kidney?

A precise definition of renin in molecular terms is not yet possible, since the enzyme has only recently been fully purified, and structural information is not yet available. To define it in functional terms can be quite misleading. Many investigators depend on an in vivo pressor response. Clearly, the number of potential substances giving such a response is great; even if it can be demonstrated that this response is mediated by angiotensin II, renin need not be involved. If the in vitro production of angiotensin I from renin's protein substrate, angiotensinogen, is accepted as the sole criterion, one may be misled; other enzymes may degrade this substrate in the same way. For example, pepsin cleaves renin substrate to produce angiotensin I [18]. Neutralization

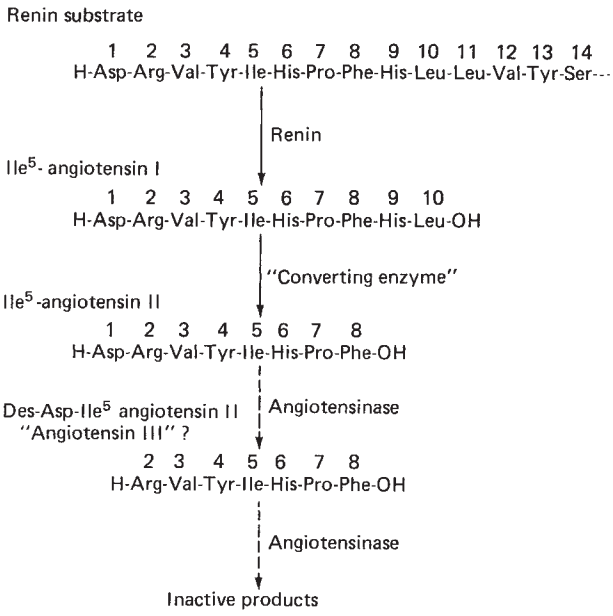

Fig. 1. *Biochemistry of the renin-angiotensin system.* Ile^5-angiotensin contains isoleucine in the 5 position and is the form of peptide that occurs in man. The existence of des-Asp^1-angiotensin II as an intermediate in the pathway has not been definitely established. (Data taken from Ref. 14. Reprinted by permission from the *New England Journal of Medicine*.)

of enzyme activity by antibodies is used as another criterion of identification, but may also be misleading because most of the antigens utilized in eliciting antibody have been relatively impure mixtures. It is conceivable that antibodies to several different enzymes may be present in the antisera used. Although antibodies specific for highly purified mouse submaxillary gland renin that cross react with mouse plasma renin are available [19], it is not at all certain that they possess unique specificity for this enzyme. Related acid proteases may share common antigenic determinants. The close relationship of the catalytic sites of this set of enzymes has already been defined by the demonstration that pepstatin inhibits the action of a number of seemingly unrelated proteases, such as pepsin, rennin, cathepsins A and D, and renin [20, 21].

Are there prorenins?

Larger molecular size renins in the kidney. Some of the earliest accounts of purification attempts of renin suggested multiple components. Skeggs et al [22] in 1967 demonstrated that hog renin prepared at pH 7.0 was converted by exposure at pH 2.4, or by longer exposure at pH 5.0, to an enzyme of higher specific activity but similar Michaelis constant. Subsequently, the same group showed that human kidney renin could be isolated in multiple molecular forms, all of which had approximately the same mo-

lecular weight (approximately 39,500 daltons) [23]. Most recently, this group [24] reexamined hog kidney and found that whether kidney was extracted at a neutral or at an acid pH, a relatively constant fraction of higher molecular weight material (57,000 to 59,000 daltons) was observed on gel filtration. This material comprised about 20% of total renin activity; it could neither be activated nor changed in its molecular size by exposure to acid.

In contrast, a number of other investigators demonstrated the presence of a high molecular weight form of renin, which could be shown to increase in enzymatic activity by acid exposure. In some instances, this increase in activity was accompanied by a decrease in molecular weight. In other reports, apparent molecular size did not change with activation. Rubin [25] observed an activation of renin activity in crude extracts of hog kidney on acidification. This activation could not be demonstrated with more purified materials, suggesting the participation of a protease. Lumbers [26] demonstrated a marked increase in renin activity in human amniotic fluid after acidification. Skinner et al [27] confirmed this observation and indicated that approximately 80% of the renin present in amniotic fluid was inactive and could be activated by acidification. Morris and Lumbers [28] separated renin activity from the activating factor. At pH 1.5 renin is denatured, but an activating principle remains, which when added to relatively inactive renin can increase its specific activity. Trypsin and to a lesser extent chymotrypsin were also shown to activate renin. Later Morris and Johnston [29] isolated renin-containing particles from the rat kidney by isopyknic gradient centrifugation and showed that these particles contained a relatively inactive form of renin that could be activated by acid treatment. As in all other reports, the molecular size of active renin was close to 40,000 daltons (37,000 daltons in this instance). Morris and Johnston suggested that the inactive form of renin was only of slightly greater molecular weight (44,000 daltons).

Boyd [30] was careful to extract hog kidneys at a neutral pH in order to avoid acid activation early in the purification procedure and observed two forms of renin, one having molecular weight of 60,000 daltons and the other 40,000 daltons. The larger molecular weight renin was characterized by an attenuated and more prolonged pressor response in vivo than the lower molecular weight form. Acidification to pH 2.5 at 4° C increased the pressor response of the higher molecular weight renin, but did not change that of the lower molecular weight form. This activation could be effected by high concentrations of sodium chloride and several chaotropic agents. Activation could also be effected simply by diethylaminoethyl (DEAE)-cellulose chromatography. All of these maneuvers decreased the molecular size of renin as it was activated. A fraction could be isolated on DEAE-cellulose chromatography, which combined with the lower molecular weight active form of renin to increase its molecular size and decrease its activity. Leckie and McConnell [31] reported very similar observations on rabbit kidney renin. As in Boyd's report, renin was quantified by in vivo pressor response. The active form of renin had a molecular weight of 37,000 daltons, the inactive form 55,000 daltons. Acid treatment of the inactive form reduced its molecular size to that of the active form and increased pressor response in vivo. An inhibitory fraction of 13,000 daltons was isolated by DEAE-cellulose chromatography. Upon addition of this fraction to active renin, a time-dependent drop in renin activity could be demonstrated with a concomitant increase in molecular size. On the basis of these observations, a noncovalent association between renin and inhibitory protein was implied.

Slater and Haber [32] extracted human kidneys at neutral pH in the presence of several protease inhibitors. They demonstrated a fraction possessing renin activity that had a molecular weight of 63,000 daltons by gel filtration. This fraction could be further purified by column chromatography and affinity chromatography on a (D-Leu^6) octapeptide column [33], which yielded a purified product having the same molecular weight. Acidification of the larger molecular weight form of renin early in the purification process followed by gel filtration resulted in an increase in total renin activity. Following further purification, however, acidification did not alter renin activity, suggesting that activation was effected by a protease that was removed during the purification procedure. These investigators were able to relate the two renin activities by demonstrating that antibodies raised to the larger molecular weight form of renin inhibited activities of both forms. Inagami and Murakami [34] demonstrated three forms of renin from hog kidney having molecular weights of 140,000, 61,000 and 42,000 daltons. Great care was taken in the extraction procedures to avoid action of endogenous proteases or exposure to acidic pH. Higher molecular weight forms were purified by affinity chromatography, gel filtration, and ion-exchange chromatography to homogeneity by both polyacrylamide gel electrophoresis

and electrofocusing. The specific enzymatic activity of the 61,000 dalton form of renin was 9% as active as the 42,000 dalton form of renin on a molar basis. The largest form of renin (mol wt, 140,000 daltons) was only 0.03% as active on a molar basis as fully active renin. These investigators have not yet reported on the interconversion among the various forms.

Larger molecular size renins in plasma. Sealey and Laragh [35] observed an increase in PRA in the plasma of normal subjects and of patients with essential hypertension after prolonged storage of the plasma at −20° C. More recently, these investigators [36] report that activation can occur on storage of human plasma for 4 days at −5° C and pH 7.4, and that activation may be mediated by proteases [37]. Leckie and McConnell [38] show similar activation of human plasma by acidification. Day and Leutscher [39] demonstrated a higher molecular weight form in some human plasmas (approximately 63,000 daltons) that differed in size from normal plasma renin (43,000 daltons). Exposure of the higher molecular weight renin at pH 3.0 to 3.6 or brief incubation with pepsin resulted in a tenfold increase in enzymatic activity. This larger form of renin was also found in tumor extracts and in amniotic fluid, but was not present in normal plasma or kidney extracts. Patients with certain disease states, such as hypertension associated with renal tumors or diabetes with neuropathy, also showed evidence of the larger molecular weight form of renin in their plasma [40, 41]. In their hands, acid activation did not significantly alter the molecular size of the higher molecular weight form of renin coincident with activation [39]. Derkx et al [42] demonstrated that an inactive form of renin was released by the kidney in patients with renal artery stenosis. Isoproterenol, tilting or diazoxide, in both normotensive and essential hypertensive individuals increased the concentration of the active form of plasma renin and reduced that of the inactive form. An inverse physiological relationship between inactive and active renin was suggested.

Malling and Poulsen [19] measured high molecular weight forms of renin in plasma both by enzymatic activity and direct radioimmunoassay using an antibody elicited by highly purified mouse submaxillary gland renin. Three components were found: the well-recognized active renin at an apparent molecular weight of 40,000 daltons; a 70,000 dalton form; and an 800,000 dalton form. The specific activity of the higher molecular weight forms was considerably less than that of the 40,000 dalton form when the amount of renin measured by enzymatic assay was compared to that quantified by the direct radioimmunoassay. Most recently, Nielson, Malling and Poulsen [43] demonstrated that the 800,000 dalton form can be converted to the active 40,000 dalton form by storage, exposure to acid, and limited proteolysis. The 70,000 dalton form can be activated by acid and limited proteolysis. The 70,000 dalton form, however, does not change molecular weight with activation.

How can these contradictory data be resolved? Certainly some differences can be accounted for by the action either of renal proteases on the components being studied or artifactual ex vivo association among proteins. Discrepancies in molecular size, covalent integrity of larger forms of renin, and either facility or failure to demonstrate interconversion of larger to smaller molecular weight forms may well be related to the care various investigators have taken either to exclude protease activity or to prevent nonspecific aggregation from occurring in the course of preparation. In evaluating these reports, it is prudent to question whether or not the enzymatic or biological activity being studied is renin or that of another enzyme that releases angiotensin. Alternatively, all the large molecular weight forms examined in plasma may simply represent the association of renin with one or another carrier protein. It is only through examination of highly purified materials and detailed molecular or immunologic characterization that the very important question of whether or not renin has several larger molecular weight biosynthetic precursors can be answered.

Determinants of renin secretion in normal man. In the normal unstressed individual, the major determinants of renin secretion are posture, sodium intake, and time of day. In a study of normal controls [44], very low levels of both renin activity and plasma aldosterone concentration were observed at the highest sodium intake, 240 mEq/day. There seemed to be little variation during the course of the day. At 100 mEq sodium intake, renin activity was low during sleep but rose by a factor of nearly 10, reaching a maximum by the middle of the day. By 8 P.M., it declined to early morning levels, even though the subjects remained upright at normal activity throughout this period. Plasma aldosterone levels followed renin activity faithfully. At a low sodium intake, 10 mEq/day, nighttime levels of both renin and aldosterone were higher and plasma aldosterone seemed to peak at a still higher level. On the other hand, plasma cortisol, which reflects

adrenocorticotropic hormone (ACTH) secretion, followed a different and independent diurnal pattern. Cortisol peaked at 8 A.M. and gradually fell during the course of the day. Its cycle was not at all correlated with either renin or aldosterone, and the magnitude of peak plasma concentration was independent of sodium intake. If normal individuals were kept in bed for 24 hours, diurnal cycles of renin secretion could still be observed, but the height of the peaks was considerably blunted [45, 46].

Inhibitors of the renin-angiotensin system

The ability to measure renin activity and angiotensin II concentration by radioimmunoassay proved to be most helpful to the physiologist and clinical investigator in understanding the response of the renin-angiotensin system to a variety of interventions. It was not until specific inhibitors were available, however, that it became possible to define precisely the role of renin in any given physiologic or pathologic situation. Inhibitors may (*1*) interfere with the action of renin on its substrate, (*2*) block converting enzyme in its action on angiotensin I to produce angiotensin II, and (*3*) compete in the interaction of angiotensin II with its receptor site in blood vessels or in the adrenal cortex (Fig. 2).

Renin inhibitors. Antirenin antibody was the earliest inhibitor used in physiologic studies [47, 48, 49]. The removal or inactivation of renin from the circulation with a specific antibody should also remove whatever physiologic consequences its presence might engender. Antirenin antisera lowered blood pressure in experimental renovascular hypertension, but the specificity of the antibody, and consequently the interpretation of the results, was uncertain. Since extracts of kidney of varying purity were used as the immunogen, the antibodies produced were likely to be highly heterogeneous. One would expect to find antibodies directed against a variety of renal cellular constituents, including functionally important membrane structures and receptors. Such antibodies may simultaneously affect several of the kidney's functions, thereby obscuring or distorting the result of their inhibition of renin. Even if functionally homogeneous renin antibodies were available, the reaction of this antibody with its antigen would lead to the formation of immune complexes, which in turn could activate the complement system. A number of peptides released in the course of complement activation have independent vascular effects, again confounding the investigator. If the antibody were raised in a heterologous species, it may only be used for a short time because the formation of antibodies to a foreign protein would result in rapid elimination as immune complexes.

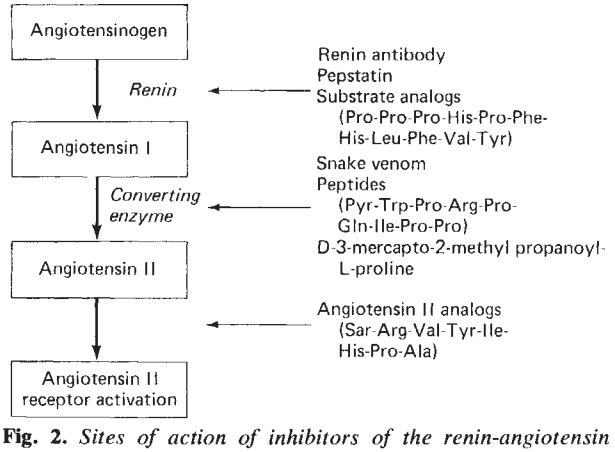

Fig. 2. *Sites of action of inhibitors of the renin-angiotensin system.*

Pepstatin is a nonspecific acid protease inhibitor that also inhibits renin activity [50]. Conflicting data in earlier experiments cast doubt on its efficacy in vivo [51]. Most recently, Menard et al have solubilized pepstatin by the addition of a hydrophilic residue to the C-terminal part of the molecule [52]. This resulted in a 100-fold increase in water solubility. Inhibitory constants for soluble and native pepstatin did not differ significantly using either native angiotensinogen or the synthetic tetradecapeptide as a substrate with hog, rat, and human renin as the enzyme. Solubilized pepstatin was effective in vivo in decreasing blood pressure that had been raised in binephrectomized rats with purified hog renin. A fall in blood pressure was also noted when the inhibitor was injected into rats rendered hypertensive by ligation of the aorta between the renal arteries. Thus a novel approach is available in the use of modified pepstatins in investigation of the renin-angiotensin system.

A new class of competitive renin inhibitors based on substrate structure has now been synthesized [53, 54]. Skeggs et al reported that octapeptide I (His-Pro-Phe-His-Leu-Leu-Val-Tyr) was the shortest peptide that was able to act as a substrate for renin and also could be shown to be a competitive inhibitor of the renin-tetradecapeptide substrate reaction [55, 56].

Poulsen, Burton and Haber [54] synthesized a number of analogs that exhibited stronger inhibitory effects than the parent octapeptide. The most successful of the first group was characterized by substitution of the D-stereoisomer of leucine at position

6 (His-Pro-Phe-His-Leu-D-Leu-Val-Tyr), immediately carboxyterminal to renin's cleavage site. At pH 5.5, its inhibitory constant with respect to the tetradecapeptide substrate was 3 μmoles and with respect to the protein substrate in plasma, 32 μmoles. The D-Leu substitution prevented cleavage of the Leu-D-Leu bond by renin. Unfortunately, this inhibitor was inactive at pH 7.4 and could not be used in physiologic studies. Other analogs that were soluble and active at physiologic pH were then synthesized [53]. The most potent of these (Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr) is characterized by phenylalanine substitutions for the leucine residues at either side of the cleavage site and a proline residue at the amino terminus of the peptide. This compound was capable of inhibiting the action of renin on both the tetradecapeptide and on its natural protein substrate in plasma at pH 7.4 with nearly equal effectiveness.

Converting enzyme inhibitors. A series of peptides originally isolated from snake venom are effective inhibitors of angiotensin-converting enzyme [57]. They act to block the cleavage of angiotensin I and thereby prevent the formation of angiotensin II [58]. The synthetic nonapeptide Pyr-Trp-Pro-Arg-Phe-Gln-Ile-Pro-Pro (Teprotide), based on the structure of one of the natural snake venom peptides [59], has now been used in both animal and human studies, which will be described in detail subsequently.

More recently, a new inhibitor of converting enzyme has become available. Ondetti et al [59] reported the synthesis of D-3-mercapto-2-methylpropanoyl-L-proline (captopril), a relatively low molecular weight compound which inhibits angiotensin-converting enzyme after oral administration [60]. The application of this material in a clinical study will be detailed later.

Competitive inhibitors of angiotensin II. Sarcosine^{1}alanine^{8}-angiotensin II (Saralasin) [61], (Fig. 2) is an example of a series of effective and specific inhibitors [62] that compete with angiotensin II at its receptor sites. These peptides are based on variants of the structure of angiotensin II. The critical site of amino acid substitution, which determines the efficacy of an inhibitor, is the carboxyterminal position; substitutions at the amino terminal position serve to enhance activity. These compounds have now found both experimental and clinical applications [63–70].

Renin and sodium balance

The i.v. infusion of converting enzyme inhibitor (CEI) has no discernible effect either on blood pressure or PRA in a normal experimental animal maintained on adequate sodium intake [71–73]. The angiotensin II competitive inhibitor Saralasin results in a brief pressor response in the normal animal, followed by prompt return of blood pressure to normal levels even though infusion of the drug may continue [63, 64].

Sodium deprivation, however, uncovers a very different response [64]. We studied trained conscious animals that had undergone prior adrenalectomy and were subsequently maintained on 25 mg of cortisone and 1 mg of desoxycorticosterone acetate [74]. On a normal intake of sodium (50 to 60 mEq/day), CEI did not lower blood pressure. On an intake of 10 mEq of sodium per day, however, very different results were obtained. Baseline blood pressure levels were within the normal range. The animal was alert and manifested normal activity and behavior. Plasma renin activity was moderately elevated. Upon administration of Saralasin, blood pressure levels first increased 25 mm Hg and then decreased 27 mm Hg below control levels. These hemodynamic changes were associated with a striking rise in PRA. Blood pressure soon returned to control levels coincident with a fall in renin activity. The subsequent administration of CEI resulted in a prompt decrease in blood pressure to the same degree without the initial increase noted when Saralasin was used. Renin activity also increased coincidentally with the hemodynamic change in response to both inhibitors. The results of these experiments are consistent with earlier and subsequent reports [61, 63, 64, 66, 67, 71, 72, 73, 75].

A decrease in blood pressure in a sodium-depleted animal consequent to blockade of the action by renin by two very different methods suggests that, in the presence of a limited extracellular fluid volume, the hormone plays a major role in blood pressure maintenance. Is the immediate rise in renin activity simply the result of baroreceptor stimulation or reflex increase in sympathetic activity secondary to a lowered blood pressure? Or are other mechanisms involved? An answer is suggested by the following experiment [74]. A prolonged infusion of CEI in a sodium-depleted adrenalectomized dog resulted in hypotension throughout the duration of the infusion. Renin activity increased until it reached levels 12 times greater than that found in the control period. When angiotensin II was infused at a sufficient rate to maintain normal blood pressure during the CEI infusion, renin activity did not increase. These results indicate that if both blood pressure

and angiotensin II concentration are maintained, CEI alone does not alter PRA. If the alpha-adrenergic agonist phenylephrine, which itself has no effect on renin activity, is used to maintain blood pressure instead of angiotensin II during CEI blockade, an increase in renin activity still occurs, though to a somewhat lesser degree. To exclude reflex beta-adrenergic stimulation as a cause of renin release, a blocking dose of propanolol was given prior to the injection of the inhibitor. Even though heart rate did not change as blood pressure decreased, PRA increased significantly. These experiments indicate that the rate of renin secretion is controlled by both blood pressure and angiotensin II concentration. These observations confirmed earlier experiments that demonstrated negative feedback of angiotensin II concentrations onto renin secretion rates both in humans [76] and in other species [77–80]. Blair-West et al [81] showed that this inhibition could be demonstrated at physiologic concentrations of the hormone and that it was independent of changes in renal arterial pressure and sodium concentration. More recently Freedman, Davis, and Lohmeier [82] demonstrated that PRA decreases during infusion of either angiotensin II or the heptapeptide des-1-Asp-angiotensin II at rates that do not significantly affect renal blood flow, arterial blood pressure, or sodium excretion.

Studies in normal human subjects

Does the renin-angiotensin system come into play only at the extremes of extracellular fluid volume depletion, or does it also have a role in blood pressure regulation at lesser degrees of physiologic stress? Studies in human subjects have addressed this question [83]. Four normal young subjects in sodium balance with a 110 mEq/day intake were first studied in the supine position, then tilted upright to 70° before and after administration of CEI. The nature and duration of the tilting stress was judiciously chosen so that none of the subjects would become either hypotensive or faint. During the study, heart rate and blood pressure were monitored and frequent blood samples were obtained for PRA and aldosterone concentration.

As can be seen from Figure 3, prior to the administration of CEI, upright tilting resulted in little hemodynamic change, a minimal narrowing of pulse pressure, and a slight tachycardia; however, a rise in both PRA and plasma aldosterone concentration occurred. The administration of CEI did not result in significant hemodynamic changes either in the su-

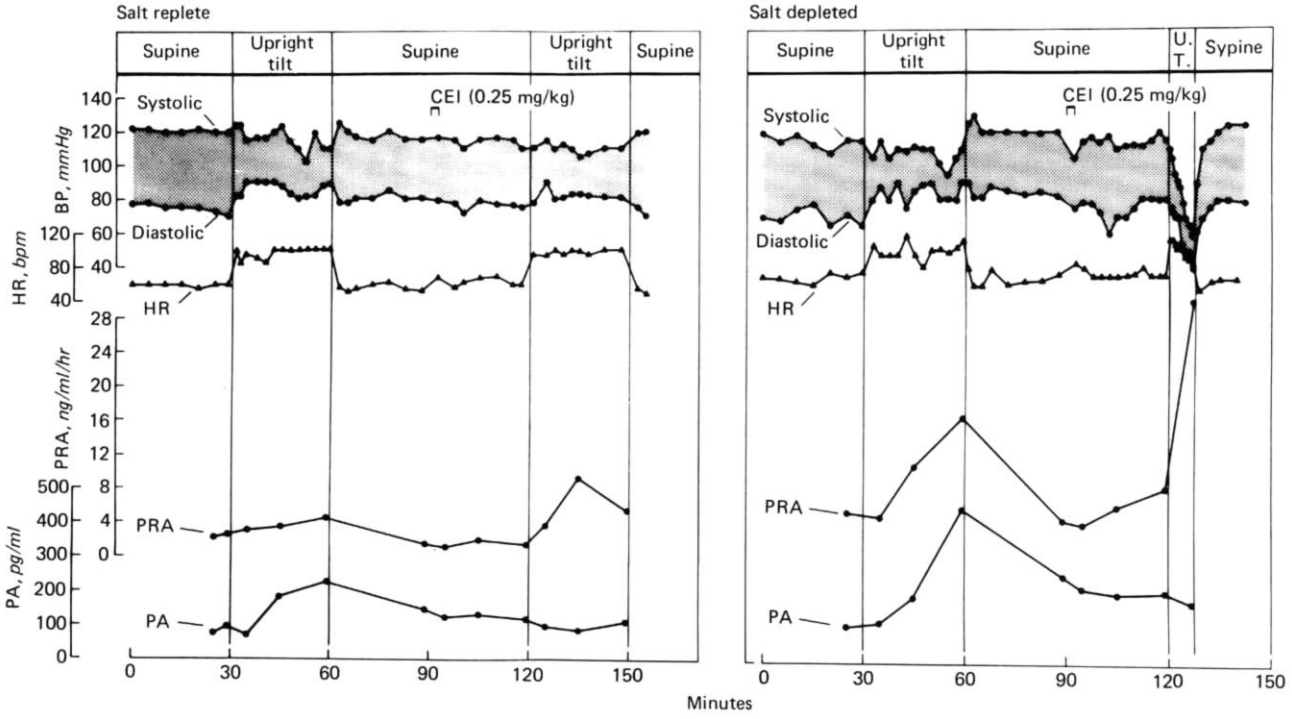

Fig. 3. *Representative example of a subject examined in the supine posture and during tilting while sodium-replete and sodium-depleted prior to and subsequent to the administration of converting enzyme inhibitor (CEI). BP* = blood pressure; *HR* = heart rate, *PRA* = plasma renin activity, *PA* = plasma aldosterone. (Data taken from Ref. 83. Reprinted by permission from *Circulation*.)

pine position or on tilting. Renin activity increased both in the supine position and on tilting, but no corresponding rise in aldosterone concentration was apparent. After sodium depletion either by diet or after the administration of a diuretic, an average weight loss of 2.6 kg was observed. Supine renin and aldosterone plasma values were higher during the control period; the hemodynamic response to tilting was somewhat more marked under these circumstances than with the higher sodium intake. After administration of CEI, tilting was associated with a striking decrease in blood pressure to hypotensive levels accompanied by an even greater elevation in renin activity; there was, remarkably, no change in plasma aldosterone concentration.

To determine the effects of prolonged infusion of CEI in the supine posture, another group of five normal subjects was given 80 mg of furosemide; they sustained a weight loss of 1.54 kg. The subsequent administration of CEI was followed by a transient drop in diastolic blood pressure associated with a brief tachycardia. Blood pressure and heart rate returned to control values and remained there during a constant infusion of CEI for the next 145 minutes. Renin activity increased rapidly to very high levels immediately after the initiation of CEI infusion. At the same time, plasma aldosterone values decreased.

These observations in normal man given CEI extend and reinforce the conclusions of earlier experiments in sodium-depleted animals. A marked decrease in blood pressure and an increase in heart rate on tilting in sodium-depleted but not in sodium-replete subjects, indicates that angiotensin II is an essential element of blood pressure control, even in states of only modest extracellular fluid volume depletion. The increase of PRA in the supine position subsequent to CEI infusion, in the absence of a decrease in blood pressure, suggests that angiotensin II exerts direct feedback control on renin secretion. The absence of the expected increase in plasma aldosterone concentration after CEI infusion, both on tilting or sodium depletion in the presence of an exaggerated renin activity, suggests that angiotensin II is the primary stimulus to aldosterone secretion in response to sodium depletion or postural change.

Experimental renovascular hypertension

The role of renin in the genesis and maintenance of renovascular hypertension has been subject to conflicting interpretations and, at times, apparently irreconcilable experimental data. An elevation in renal vein renin activity has proved to be a most useful diagnostic test for curable unilateral renal artery stenosis. Yet in chronic experimental or clinical renovascular hypertension, PRA is often normal.

Acute experimental studies are difficult to interpret because anesthesia, surgical trauma, and blood loss all modify the response of the renin-angiotensin system. Renal function has been shown to be altered as long as 1 to 2 weeks after surgery [84]. To circumvent some of these problems studies were performed on trained, conscious animals appropriately prepared and examined at least 2 weeks subsequent to surgery [84]. The animals had undergone unilateral nephrectomy. An external catheter allowed inflation of a cuff around the renal artery while catheters proximal and distal to the cuff permitted precise adjustment of the gradient created by this stenosis. Blood samples could be obtained either in the renal vein or in the vena cava.

A substantial gradient was established between the aorta and the renal artery and was maintained at a constant level by adjustment of the cuff [71]. A rapid increase in mean aortic pressure to hypertensive levels occured and was associated with an early elevation of PRA. The administration of CEI resulted in a prompt decrease in blood pressure to near normotensive levels associated with a striking increase in PRA. These observations indicated that the renin-angiotensin system was responsible for the initial increase in systemic blood pressure that results from renal artery constriction. Blockade of the conversion of angiotensin I to II promptly reduced blood pressure to normal.

When renal artery constriction was maintained over a longer period persistent hypertension resulted, but PRA remained elevated for only a few days, returning to control levels as sodium and water retention occurred [84]. If angiotensin II levels are prevented from increasing by continuous administration of CEI after renal artery constriction, blood pressure does not increase over a 4-day period in a conscious one-kidney dog with renal artery constriction [72]. Once hypertension is established however, inhibitors have little effect, indicating that angiotensin II may not play a significant role in the maintenance of chronic hypertension in the one-kidney experimental preparation [61, 85, 86, 87]. Typical of these experiments is the study of Bumpus et al [75] who reported that blockade with Saralasin was effective in reducing blood pressure in the conscious dog within 3 to 6 days after renal artery constriction, but not later. Similarly, Johnson et al [66] reported that Saralasin did not lower blood

pressure in one-kidney Goldblatt dogs 2 to 7 weeks after constriction of the renal artery. Thus, the decreasing effectiveness of CEI and angiotensin II antagonists in lowering blood pressure in chronic one-kidney renovascular hypertension suggests that over time other factors begin to play an increasingly important role in the maintenance of elevated blood pressure.

What are these contributing factors? Tobian, Coffee, and McCrea [88] and Guyton, Coleman, and Granger [89] have stressed the importance of sodium and water retention in the maintenance of the elevated blood pressure of chronic renovascular hypertension. Tagawa et al [84] directly demonstrated sodium retention and increased water intake following the chronic constriction of the renal artery in a unilaterally nephrectomized dog with a normal sodium intake. Gavras et al [64] showed that in the sodium depleted one-kidney Goldblatt rat, Saralasin resulted in a large decrease in blood pressure, whereas after sodium repletion no decrease in blood pressure could be demonstrated with this agent. More recently, Rocchini and Barger produced reversible renal artery stenosis in seven trained, unanesthetized dogs maintained on a diet containing less than 10 mEq of sodium a day [90]. Renal artery perfusion pressure was reduced to 60 to 70 mm Hg, and blood pressure increased 37 ± 4 mm Hg within 1 hour of constriction, remaining at this level throughout the experiment. Presumably because of the low sodium intake, fluid and sodium retention did not occur, as confirmed by balance studies. There was no change in hematocrit, weight, or plasma volume. Plasma renin activity as well as plasma aldosterone concentration increased and remained elevated through 14 days of study. At the end of 14 days, the animals were exquisitely sensitive to CEI. In contrast to animals on an ad lib sodium intake, which are unresponsive to CEI, blood pressure returned to normal within 5 minutes of an i.v. bolus injection of the drug. Thus, unlike the findings in experimental models in which a normal sodium intake is permitted, when sodium and fluid accumulation is prevented by dietary sodium restriction one-kidney renovascular hypertension is characterized by a persistently elevated renin activity. The evidence, therefore, seems to point to sodium and water retention as the principal factors in the maintenance of persistent hypertension in the one-kidney animal with renal artery constriction.

There seem to be two phases of renovascular hypertension: (1) an initial phase in which elevated blood pressure is maintained by the direct pressor actions of angiotension II; and (2) a later chronic phase in which blood pressure is maintained largely as a result of hypervolemia, mediated by sodium and water retention. Whether sodium retention is simply the direct effect of diminished renal arterial pressure on kidney function or whether it is mediated indirectly via angiotensin II through its action on mineralocorticoid secretion remains to be determined.

The long-term role of renin in mediating sodium retention and hypertension in one-kidney renovascular hypertension has recently been tested by Watkins et al [91]. The administration of Saralasin or CEI to one-kidney renovascular hypertensive dogs did not block the development of blood pressure elevation suggesting a lack of participation of the renin-angiotensin system under these circumstances although some of their experimental interpretations can be challenged, Skeggs et al [85, 92, 93] came to similar conclusions. They showed that hypertension in a one-kidney rabbit model could not be ameliorated by renin-specific antibody nor by the angiotensin II inhibitor Saralasin. They did, however, demonstrate that blood pressure could be lowered to normal by immunization with a hog kidney cortex preparation that did not contain renin. The passive transfer of antibody preparations specific for this material had the same effect. When renal cortex preparations were injected directly, a delayed slow increase in blood pressure occurred that persisted indefinitely, even after the injections were stopped. Skeggs et al postulate the participation of a new hypertensive substance they named renopressin.

Boucher et al have isolated an enzyme, tonin, from the rat's submaxillary gland that acts directly on renin substrate to release angiotensin II without the intermediate prohormone angiotensin I [94]. It has been fully purified recently and shown to be different from renin. Administration of rabbit tonin antiserum resulted in a decrease in blood pressure to normal in 7 of 10 one-kidney hypertensive animals, whereas very little change in blood pressure was observed in two-kidney, one-clip hypertensive animals or in a control group [95]. These workers postulate that in rabbits with chronic one-kidney hypertension tonin might be the responsible mediator. It is difficult to be sure whether or not tonin is the same substance as the renopressin of the Skeggs investigations. In any event, further detailed characterization of these factors is needed before they can be implicated with certainty in the etiology of experimental renovascular hypertension.

Renin-dependent hypertension in human subjects

Although the etiologic role of the renin-angiotensin system in chronic renovascular hypertension remains to be established, it is generally agreed that the determination of renin activity in renal venous blood is a most useful diagnostic aid. When renal vein renin activity from the affected kidney is greater than that of the uninvolved side, the probability of improvement in blood pressure after surgery is considerable [96–100].

To increase the sensitivity and reliability of renal vein sampling, a variety of stimulatory maneuvers including diuretic administration, vasodilator administration, and upright posture have been used [96, 101–105]. Most recently, Re et al [106] used CEI in the study of a series of unselected hypertensive patients undergoing bilateral renal vein catheterization. In the group of patients (group I) who were later shown to have predominately unilateral renal artery stenosis demonstrated by contrast studies, the ratio of involved to uninvolved renal PRA increased from 2.94 ± 0.91 before to 8.36 ± 2.94 after CEI administration (Fig. 4). In the group (group II) that did not have a renal artery abnormality, the ratio of the initially higher to lower side was 1.99 ± 0.49 before and 1.17 ± 0.07 after the administration of CEI, a nonsignificant difference. Plasma renin activity after the administration of CEI was predictable by the measurement of pretreatment PRA. Mean blood pressure decreased in both groups, but the decrement was predicted by PRA prior to CEI administration. Thus, CEI, probably because of its interference in the angiotensin II negative feedback loop, increases renin secretion in the affected kidney in unilateral renal artery stenosis far more than in the unaffected kidney. This results in increased diagnostic accuracy by magnifying the PRA difference between the two sides.

Several investigators have suggested that a decrease in blood pressure in response either to CEI or to angiotensin II analogs may be of value in identifying patients with renin-dependent hypertension [68–70, 107]. Gavras et al [107] stress that sensitivity of detection may increase if subjects have been previously sodium depleted. A decrease in blood pressure under these circumstances must be interpreted with the greatest caution. It may indicate only that blood pressure maintenance is in part dependent on angiotensin II, a normal physiologic state in volume- or sodium-depleted individuals. Utilization of inhibitors in the identification of renin-dependent hypertension may require that testing be carried out while subjects are in a state of normal sodium balance. For example, a 28-year-old woman with chronic bilateral pyelonephritis and persistent hypertension was studied while in sodium balance through a daily sodium intake of 110 mEq. Plasma renin activity was abnormally elevated at 8.0 ng/ml/hr (normal values using this diet are 1.02 ± 0.21 ng/ml/hr). The administration of CEI resulted in a prompt decrease in blood pressure to the normotensive range. There was a further increase in PRA accompanied by a decrease in plasma aldosterone, which confirmed blockade of angiotensin production.

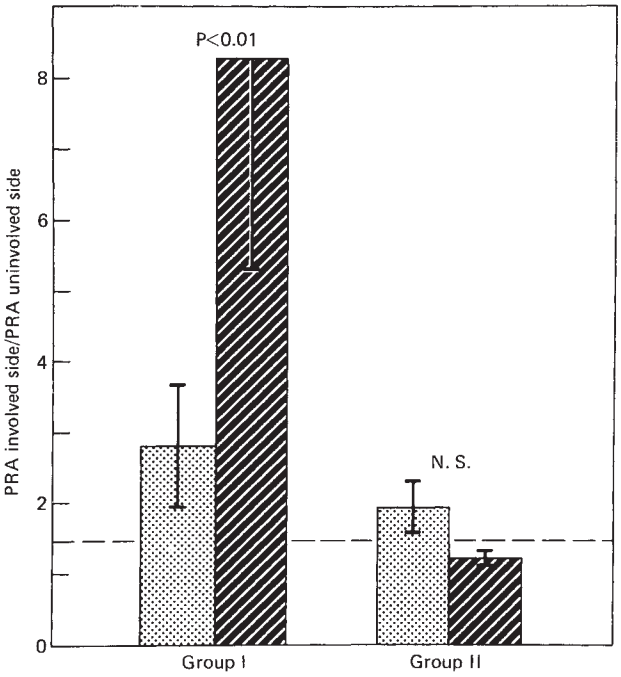

Fig. 4. *Mean (± SE) renal vein plasma renin activity (PRA) ratio before (dots) and after (diagonal bars) converting enzyme inhibitor (CEI) in Group I and Group II patients. Dashed line* indicates a ratio of 1.5. (Data taken from Ref. 106. Reprinted by permission from the *New England Journal of Medicine.*)

It is of interest that clinical studies with the oral angiotensin CEI discussed above (captopril) appear to give somewhat different results from those with the nonapeptide inhibitor. Gavras et al [108] report no significant correlation between pretreatment PRA and the degree of blood pressure decrease with this agent, in contrast to the findings of Re et al [106] discussed previously. Another interesting observation is that the oral CEI is equally effective in lowering blood pressure in renovascular hypertension and essential hypertension suggesting that, although useful in renin-dependent hypertension, it may well have other hypotensive actions independent of converting enzyme blockade. Oral CEI may

not prove to be as valuable as a diagnostic agent in the identification of renovascular hypertensives as other nonspecific converting enzyme inhibitors.

Turning again to consideration of the patient presented today, it would be desirable to determine whether or not renin is really contributing to the maintenance of his blood pressure prior to proceeding with any serious consideration of operative intervention. In the absence of antihypertensive medications and with a normal sodium intake of 100 mEq/day, CEI should be given intravenously as a test. If blood pressure decreases in the supine position, it is likely that renin is responsible for the patient's blood pressure elevation. If, on the other hand, the agent has no effect on blood pressure, it would be injudicious to pursue further diagnostic measures with respect to potential renin-secreting lesions in the lower pole of the left kidney. If the oral CEI became available to this patient, he certainly could be given a therapeutic trial; if successful, neither further invasive diagnostic measures nor operative intervention may prove necessary. But if medical management continues to be difficult or impossible, it would be highly desirable to try to incriminate the lower pole of the kidney as a source of excess renin secretion. Renal vein catheterization could be repeated after the administration of nonapetide CEI to determine whether the ratio of renin secretion among the several branches of the left renal vein was altered dramatically; if it were, an operative attack on the lower pole might be indicated. The risk to this patient's life from continued uncontrolled hypertension is likely to be greater than the risk of ablating the lower pole of a sole kidney.

Questions and Answers

DR J. J. COHEN: You raised the very interesting possibility that the increased renin secretion in this patient might be due to accelerated hypertension; in other words, that it is simply a fixed consequence of his long-standing extreme hypertension. The curious thing about this man's accelerated hypertension, as you pointed out, is the absence of evident renal disease; he has no proteinuria and no renal functional impairment. Do patients whose kidneys are spared, for whatever reason, during the course of accelerated hypertension also develop hyperreninemia. If so, how do you account for that?

DR. E. HABER: I think you have hit the nail right on the head. Patients who are hyperreninemic with accelerated hypertension almost invariably have renal damage. In my view, the cause of the hyperreninemia is diffuse renal arteriolar narrowing either on a functional or structural basis, which has the same net effect as a major stenosis in the main renal artery. The result is diminished renal blood flow and eventually renal parenchymal damage.

DR. N. E. MADIAS (*NEMCH*): It has been suggested that 40% of patients with renovascular hypertension have normal peripheral PRA. Do you know of any particular characteristics that differentiate such individuals from those with renovascular hypertension and elevated peripheral PRA?

DR. E. HABER: I agree that peripheral PRA is probably an unreliable test for renovascular hypertension exactly for the reason you state; almost half of the patients have normal values. The probable explanation is that these patients have reached the stage of their disease at which sufficient sodium and volume are retained to normalize renin activity. The hypertension has become volume dependent.

DR. J. T. HARRINGTON: Have you had the opportunity to study the effects of blocking or inhibiting agents in transplant recipients with renal artery stenosis? That would seem to be an ideal group to look at.

DR. E. HABER: We have not as yet studied renal transplant patients but would like to.

DR. J. J. COHEN: Apparently, there is some circulating activity of converting enzymes. Is there any diagnostic value in measuring the level of circulating converting enzymes?

DR. E. HABER: No, I don't think so. Measuring circulating enzymes might be of value, however, in determining the dose of an inhibitor. I know of no pathologic state in which the converting enzyme itself is limiting; that is, there are no causes of hypotension attributable to an insufficiency of the enzyme nor causes of hypertension attributable to an excess. The capacity of the system is in excess of what is needed.

DR. J. T. HARRINGTON: Has CEI been used in experimental models of acute renal failure?

DR. E. HABER: Yes, it has and there have been contradictory results. Initially, there was interest in the demonstration of a greater survival rate in animals with experimental acute renal failure treated with CEI, but the subsequent experiments have not reproduced this observation.

DR. J. J. COHEN: To return to our patient, we were intrigued with the possibility that he might have a small renin-secreting tumor in the lower pole of his solitary kidney. Surgery was discussed with him, but he has been understandably resistent to the

idea. In addition to the obvious risks, another aspect of the surgical alternative has bothered me. Knowing that the patient has had hypertension for at least 10 years, I wonder if there is precedent for a renin-secreting tumor being present over such a long period and still not being detectable by a good angiographic study.

DR. E. HABER: One of the patients reported by Conn et al [9] had 6 years of hypertension clearly due to a tumor; when it was removed, blood pressure normalized. The tumor was very small and difficult to see even during surgery. Renin-secreting tumors are generally benign and slow growing; they seldom metastasize, and they secrete a great deal of renin for their size. It is conceivable that a tumor could be present for 10 years in this patient and yet not be obvious.

DR. J. J. COHEN: Surgical intervention in a patient with a solitary kidney obviously carries considerably more risk than in a patient blessed with two kidneys. If we were able to exclude renal artery stenosis and confirm a diagnosis of renin-dependent hypertension, what would be your specific recommendations for management of the patient?

DR. E. HABER: I think the patient's prognosis is poor in view of complications already manifest. He has damage both to his central nervous and his cardiovascular systems; fortunately, he does not have renal damage yet. I would take the risk of examining the lower pole of his kidney by direct visualization if needed. Of course, a second angiographic study should be done first.

DR. J. J. COHEN: Yes, I think it should. In addition, would you consider a trial of oral CEI worthwhile in this patient?

DR. E. HABER: Yes, he may respond favorably. As I indicated, if he has a tumor it is likely to be benign and grow slowly. In a case reported by Robertson et al [8], the tumor was missed on repeated review of one angiographic study, but 2 years later it was seen on a subsequent angiogram, which means that they do grow albeit slowly. Surgery could be considered with a great deal more confidence if the diagnosis of tumor could be made by angiography.

DR. J. J. COHEN: Even if we had definite evidence that a tumor was present, the patient still has a single kidney and the operative risk is considerable. Under those circumstances, would you still attack it surgically or would you elect a medical alternative and use an oral CEI?

DR. E. HABER: There is no followup study on renin-producing tumors treated with CEI. I would, however, feel uncomfortable about leaving a diagnosed tumor in place. I would take the risk of surgery, particularly if the tumor were located at the lower pole of the kidney facilitating its removal without endangering the rest of the organ.

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The editors should like to expand the scope of these exercises by encouraging active participation of the journal's readership in *Nephrology Forum*. Questions or comments pertaining to this month's discussion may be submitted to *Nephrology Forum*, Box 212, New England Medical Center Hospital, 171 Harrison Avenue, Boston, Massachusetts 02111. Correspondence received by May 30, 1979 will be eligible for inclusion in a forthcoming installment.